MICROCOPY RESOLUTION TEST CHART

NATIONAL BUREAU OF STANDARDS-1963-A

FINAL PROGRESS REPORT

on

NEUROMAGNETIC INVESTIGATION OF WORKLOAD AND ATTENTION

Air Force Office of Scientific Research

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OCT 16 1986
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Contract F49620-82-K-0014

to

New York University

Major advances in neuromagnetic investigation of the human
brain have been made in several areas from the work under this
contract. This report will summarize them under headings describing
each area.

ADVANCES IN INSTRUMENTATION

Since the event-related magnetic field of the brain was first
observed in our laboratory in 1974 (Brenner et al. 1975) it was
clear that neuromagnetic studies would generally involve mapping the
field pattern across a portion of the scalp, to determine the nature
of the underlying neural sources. At that time our instrumentation
was limited to a single sensor based on the SQUID (superconducting
quantum interference device), so the pattern was determined by
measuring activity at one position after another in sequence. The
sensitivity of such measurements was limited by ambient field noise
at frequencies below about 3 Hz and by intrinsic sensor noise above

SECURITY CLASSIFICATION OF THIS PAGE

ADA173155

REPORT DOCUMENTATION PAGE

1a. REPORT SECURITY CLASSIFICATION UNCLASSIFIED		1b. RESTRICTIVE MARKINGS			
2a. SECURITY CLASSIFICATION AUTHORITY		3. DISTRIBUTION/AVAILABILITY OF REPORT Approved for public release distribution unlimited			
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE					
4. PERFORMING ORGANIZATION REPORT NUMBER(S) 1		5. MONITORING ORGANIZATION REPORT NUMBER(S) AFOSR.TR. 86-0913			
6a. NAME OF PERFORMING ORGANIZATION New York University	6b. OFFICE SYMBOL (If applicable)	7a. NAME OF MONITORING ORGANIZATION Air Force Office of Scientific Research			
6c. ADDRESS (City, State and ZIP Code) Departments of Psychology and Physics 4-6 Washington Place New York, NY 10003		7b. ADDRESS (City, State and ZIP Code) Building 410 Bolling AFB, DC 20332-6448			
8a. NAME OF FUNDING/SPONSORING ORGANIZATION AFOSR/NL	8b. OFFICE SYMBOL (If applicable) NL	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER F49620-82-K-0014			
8c. ADDRESS (City, State and ZIP Code) Building 410 Bolling AFB, DC 20332-6448		10. SOURCE OF FUNDING NOS.			
		PROGRAM ELEMENT NO. 61102F	PROJECT NO. 2313	TASK NO. A4	WORK UNIT NO.

11. TITLE (Include Security Classification)
Neuromagnetic Investigation of Workload and Attention

12. PERSONAL AUTHOR(S)
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13a. TYPE OF REPORT final technical report	13b. TIME COVERED FROM 1/1/82 TO 12/31/84	14. DATE OF REPORT (Yr., Mo., Day) 6/24/86	15. PAGE COUNT 45

16. SUPPLEMENTARY NOTATION

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number) selective attention, neural activity, P-300 paradigm, magnetic localization
FIELD	GROUP	SUB. GR.	

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

During the period covered by this report, we made major advances in the technology associated with neuromagnetic measurements. These included the demonstration of the effectiveness of electronic cancellation in reducing unwanted effects of ambient field noise. We also developed a high-precision sensor positioning system, designed and constructed a device for accurately positioning the subject's head under the sensors, and developed advanced software for a multi-sensor system. Experiments during this period included one in which we demonstrated modulation of the EEG coincident with the onset of the N100 component of a visual response to infrequent stimuli presented under the oddball paradigm. We collaborated on another experiment with the Cognitive Psychophysiology Laboratory of the University of Illinois in a study of P300 related to the presentation of alphanumeric stimuli. The result confirmed our earlier findings using abstract visual stimuli, i.e., the equivalent current dipole source of P300 is in or near the hippocampal formation.

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT UNCLASSIFIED/UNLIMITED ☒ SAME AS RPT. ☒ DTIC USERS ☐	21. ABSTRACT SECURITY CLASSIFICATION UNCLASSIFIED	
22a. NAME OF RESPONSIBLE INDIVIDUAL Dr. Alfred R. Fregly	22b. TELEPHONE NUMBER (Include Area Code) 202-767-5024	22c. OFFICE SYMBOL NL

DD FORM 1473, 83 APR   EDITION OF 1 JAN 73 IS OBSOLETE.   UNCLASSIFIED

SECURITY CLASSIFICATION OF THIS PAGE

that (Romani et al. 1982).

Long Baseline Neuromagnetometer

To improve sensitivity for observing subcortical sources lying
deep within the brain we developed a neuromagnetometer with a
detection coil having a much longer baseline between its individual
coils. The work was carried out by Dr. C.M. Bastuscheck in our
laboratory. The coil former was made of Macor, a new ceramic
material that just appeared on the market. It has the attractive
feature that its coefficient of expansion is close to that of the
niobium wire used to wind the coil, so that the individual turns
will continue to lie snugly within their machined channels. The
gradiometer was configured as an asymmetric second-order
gradiometer, with a 1.5-cm diameter for the pickup coil and 2.4-cm
diameter for the compensating coils. The baseline was 6 cm, whereas
our existing probe had a 3.4-cm baseline. An arrangement was
incorporated for three small superconducting tabs to be placed near
the center coil, with individual adjustment rods extending through
the top of the dewar so that their positions could be controlled
when the probe was immersed in liquid helium. These tabs are
adjusted so that the gradiometer's response to uniform fields in
three orthogonal directions is minimized, a process that is
equivalent to adjusting the "field balance" of the system.

One innovation was to mount the pickup coil on a sliding

cylinder whose axial position could be controlled with high finesse by rotating a rod extending through the top of the dewar. The purpose of this was to allow us to adjust the baseline between the pickup coil and the center coil, so that the balance of the detection coil with respect to ambient fields of uniform gradient could be adjusted. This gradiometer could thus be adjusted for field balance and for gradient balance. A commercial rf-SQUID was mounted on the probe to provide an output voltage proportional to the net magnetic flux in the gradiometer.

The high-frequency noise level of this system was determined by the rf-SQUID system, as expected. Unfortunately, the low-frequency noise below this point was considerably higher than for our SQUID system with a 4-cm baseline. The noise could not be attributed to residual field imbalance or gradient imbalance. We re-configured the gradiometer for a shorter baseline and found that the noise decreased with decreasing baseline. As the noise was relatively insensitive to gradient imbalance of the gradiometer, we concluded that the principal noise component was the second spatial derivative of the ambient field. Thus there was no advantage in using a gradiometer with a very long baseline to see deep-lying sources, because the increase in signal strength with baseline would be countered by a corresponding increase in noise level.

Electronic Cancellation of Ambient Noise

After the long-baseline gradiometer was constructed, we took
advantage of having two neuromagnetometers to investigate the
possibility of electronically reducing the effect of ambient field
noise. The procedure was to place this sensor well away from the
subject to monitor the ambient field, and to electronically subtract
its properly attenuated output (called the "reference") from the
output of the neuromagnetometer monitoring the subject. The study
was a success in that low-frequency ambient noise could be
attenuated by a factor of 5 to 10, depending upon conditions. An
example was published as Figure 25 in the review article by Romani,
Williamson, and Kaufman (1982). This demonstration made it possible
to develop multiple-sensor systems that could rely on electronic
cancellation to improve sensitivity.

With funding from the Office of Naval Research we worked with
scientists and engineers at S.H.E. Corporation in San Diego (now
named BTi Corporation) to develop a prototype system having the
capability to measure the magnetic field simultaneously at several
positions over the scalp. Such a multiple-sensor system would
greatly reduce the labor and time required to map a field pattern,
and moreover would lead to more stable results since variability in
the subject's neural activity over the course of the study would be
reduced. The prototype system (known as "Freddy") incorporates 5
SQUID sensors, arranged on a pattern with one in the center and the
others equally spaced about it. Because of the success with

electronic balancing that was demonstrated under AFOSR support, four
additional sensors were incorporated to monitor three components of
the ambient field and the axial component of the field gradient. The
electronic system was designed to allow each reference to be
attenuated by different amounts for subtraction from each of the
five signal channels. In addition, the time derivative of each
reference was obtained electronically, and these derivative
references were also individually attenuated and subtracted from
each of the signal channels. The total set of 40 attentuation values
could be adjusted by computer control.

Freddy was delivered in February, 1984, and only one week was
required to put it into operation. The five dc-SQUID sensors had
state-of-the-art intrinsic noise levels, specified by a measured
field spectral density of about 20 femtotesla per root hertz of
bandwidth. Over a period of 4 months some of the electronic
components failed and were replaced at no cost by S.H.E.
Corporation, but the SQUIDs have continued to this day to be
reliable. The electronic cancellation procedure, with four reference
signals from rf-SQUIDs, was essential to establish state-of-the-art
performance at low frequencies. Indeed, we learned that the
correlation between the references and noise in the signal channels
was sufficiently good that the noise level after cancellation was
virtually independent of the orientation of Freddy, as Scanner moved
it about the head (Williamson et al. 1984).

Helmholtz Coil Assembly

It became apparent that the process of selecting the 40
attenuator settings for the reference channels of Freddy could be
shortened if we applied a uniform ac field to Freddy in each of
three orthogonal directions separately and adjusted the settings to
minimize the output signal at this frequency. This would minimize
the output for a uniform field in any direction. We therefore
constructed two sets of square Helmholtz coils to produce fields in
two perpendicular horizontal directions, with each coil about 2
meters on a side to insure acceptable field uniformity throughout
the array of Freddy's detection coils. For the vertical field we
built a four-coil set, since we desired a much more uniform field in
that direction. We had in mind using this uniform field as part a
calibration procedure for Freddy's detection coils. That procedure
was developed in 1985 and so will not be discussed here. With
appropriate circuitry to switch the ac drive from one set of coils
to another it is now possible to determine the entire set of 50
attenuation values in less than one hour of measurements. Our
experience shows that the electronic balance remains stable for
periods of several months before the values must be re-adjusted.

Precision Positioner

While the development of Freddy was taking place, under AFOSR
support we conceived and built a novel system to move Freddy about

the head of the subject. This device was called "Scanner", and it has the virtue that the position of the sensors can be controlled with millimeter accuracy. The system was fabricated in the NYU Physics Department machine shop from fiberglass, brass, and particle board to insure that magnetic and highly conducting components would not be near the sensors.

Procedures were also developed to determine with high accuracy where measurements were made across the scalp. Accuracy in scalp position is essential for obtaining accuracy in locating neural sources within the brain. Our first step was the introduction of a device ("Halo") that would determine angular coordinates of all the measuring positions, referenced of a "head-based" coordinate system determined by head features. Halo was constructed of aluminum and stainless steel components by the Physics Department machine shop. The accuracy in determining position on the scalp in three-dimensional space is about +/- 1.5 mm with Halo. A system of physical pointers was mounted on Scanner to orient the subject, thus enabling positions indicated by Scanner to be related to positions on the scalp in the head-based system. In this way, all measurement positions over the scalp are accurately related to coordinates in the head-based system. The Halo system has proven effective for precision measurements. When combined with the use of Scanner it provides the most accurate system now available for establishing measuring positions across the head.

The successful introduction of this multiple-sensor system represents a major advance in neuromagnetic techniques. One mark of that is the acceptance of this kind of system by the neuromagnetic community. Over a half dozen similar systems are being constructed or have already been built in the United States and Europe.

Computer and Software Development

While Freddy was under development, we began an extensive program to upgrade our computer system and develop software. Graphics terminals were added as well as floppy disk drives to accommodate a larger group of users in the laboratory. Additional software had to be written so that our PDP 11/34 computer could accept nine channels of data and carry out the necessary analysis operations. Moreover it was necessary to develop algorithms that would compute the positions and orientation of every sensor, given the orientation of Freddy provided by Scanner's coordinate system. All of the algorithms for sorting positions, determining averages for multiple measurements at common positions, etc. were generalized to process multi-channel data. We also arranged hard-wire connections to the Academic Computing Facility at NYU's Courant Institute for Mathematical Sciences, so that the VAXs and Cyber 170 at that facility could be used for more extensive computations, such as determining least-squares fits for the parameters of neural sources. This required additional software development because the Courant computers use different operating systems than the PDP

11/34. Computer time at Courant has been provided by NYU at no cost to AFOSR.

EEG MODULATION STUDIES

We have explored the relationship between event-related neural activity and spontaneous activity of the brain as indicated by the EEG. This extends earlier work by Kaufman and Locker (1970) and by Spekreisje and Reits (1980). Specifically, we investigated whether event-related neural activity modulates the ongoing background EEG. The study was set up in the context of a classic odd-ball paradigm to observe P300 in which infrequent auditory tones were interleaved within a train of frequent visual stimuli. A second set of experiments were carried out with the modalities reversed. The full set of measurements were carried out by Sarah Curtis, Graduate Research Assistant. For all but one subject the odd ball stimuli (visual or auditory) usually (though not always) showed an elevated P300. For visual stimuli all subjects showed a depression in spontaneous activity in the alpha band immediately following N100, and this depression persisted for about 500 msec when the visual stimulus was an odd ball. If the visual stimulus was frequent, the depression of alpha band was present but was quickly restored to baseline after about 100 msec.

To obtain these results the ongoing EEG activity in the alpha band had to be separated from the stimulus-locked activity. This was

done by stringing together all the recorded intervals of fixed
length following each stimulus. Then the stimulus-locked features
were removed from the string by computing the Fourier series for the
string (its fundamental period is the interval) and subtracting this
periodic function from the record. What remains is the "noise" that
was not harmonically related to the stimulus. Fast fourier
transforms showed that this "noise" was large confined to the alpha
band. The noise was then rectified within each interval, and the
data for the intervals were averaged together. This average revealed
the invariant waveform for odd-ball trials and for frequent trials,
but they differed in shape and duration. When the "noise" alone was
averaged without rectification there was no response at all, thereby
proving that the background activity was indeed modulated by the
visual event. Only the visual stimulus was capable of eliciting this
modulation. Neither the odd-ball auditory stimulus or frequent
auditory stimulus produced such an effect.

It is interesting that the modulation occurs coincidentally
with N100 and is not further modulated by P300, which may suggest a
cortical origin. Apparently, if the incoming sensory signal is not
"interesting" (as in the case of frequent stimuli) the inhibition is
of limited duration; however, if the incoming visual signal is an
odd ball ("interesting"), then the visual cortex may well be
conserving its capacity to respond by not returning to its normally
active state. Indeed this study will soon be followed up with

neuromagnetic measurements over the occipital areas to locate the
sources being modulated.

MAGNETIC DETECTION OF MULTIPLE SOURCES

It is well established that many different areas of the brain
respond to visual stimulation in various species of animals. These
so-called extrastriate areas include the medial temporal (MT) region
of the macaque monkey, and other areas as well, depending upon the
species. Evidence exists that cells in some of these extrastriate
areas are particularly responsive to moving patterns. We have
undertaken a series of studies of visually evoked responses to
search for magnetic fields associated with changes in speed of a
moving grating pattern. A field pattern was observed that suggests
the existence of similar extrastriate activity in humans.

The work was done during the 5-month participation of Olli V.
Lounasmaa, Research Professor of the Academy of Finland and Director
of the Low Temperature Physics Laboratory of the Helsinki University
of Technology. Professor Lounasmaa had just organized a
neuromagnetism group at the Helsinki University of Technology. evoke
magnetic fields whose distribution suggests the existence of similar
extrastriate areas in humans.

Software was developed to present a sinusoidal bar grating on
an oscilloscope screen and cause it to drift across the screen. The

mean luminance and luminance contrast of the grating were adjustable parameters. The speed of the grating was changed sinusoidally as it drifted, the modulation being expressed as a "velocity contrast" of 50%, giving the modulation amplitude as a percentage of the average velocity. Psychophysical thresholds for detecting a change in speed were obtained for this kind of stimulus by Kaufman and Williamson (1984). In the neuromagnetic study the moving grating had a spatial frequency of 1.5 c/deg for one subject (SW) and 3 c/deg for another (PL). The average luminance was 49 cd/m^2, and the luminance contrast of the grating was nearly 100%. The gratings were caused to drift with an average speed of 3 or 5 deg/sec toward the left or the right of the subject. The frequency of modulation of the speed was 7 Hz. Thus when fixating at a black dot at the center of the screen, the subject saw a bar grating drifting in one direction and its speed changed from slow to relatively fast 7 times per second. This modulation frequency served as a reference signal for recovering responses through signal averaging with the steady-state paradigm.

A single-sensor neuromagnetometer was used to measure the evoked field at various positions normal to the scalp. The output of the SQUID electronics was applied to a comb filter to reduce coherent noise at the power line frequency and then to a bandpass filter with 48 db/octave rolloff on either side of 7 Hz. The output of the filter was sent to a signal averager, and the phase lag and amplitude of each response, after one minute of averaging, were

recorded. The occipital region and right hemispheres of two subjects (SW and PL) were studied in detail with two or more measurements at about 65 positions for each. Responses were observed over a wide area of the scalp from the occipital pole anteriorly to the central region. By studying how these responses varied with stimulus conditions it was possible to differentiate between activity associated with primary striate cortex in the visual area and extra-striate cortex in the more anterior areas.

Strong responses observed over the occipital area can be associated with sources in the primary sensory areas of the left and right hemispheres. An equivalent current dipole in each hemisphere near the midline, aligned approximately perpendicular to the longitudinal fissure and pointing toward each other, account for the field pattern over the occipital and parietal regions. In fitting these sources to the observed field pattern we imposed the constraint that they have equal stength, depths and phase lags, and we adjusted the orientation of the left hemisphere source slightly so that the rostral domain of its field pattern largely cancels the oppositely directed rostral domain of the right hemisphere source.

Source in the Central Sulcus

To search for non-occipital neural sources we introduced what we have called the piranha method: taking the observed field pattern and subtracting from it the pattern computed for each neural source

as identified. The field patterns calculated for the occipital
dipoles are comparatively weak in the area of the central sulcus.
When this predicted pattern is subtracted from the data a remarkable
feature emerges there: two domains of relatively strong responses
but opposite field direction. It is reasonable to identify this pair
of domains as arising from a source that may be modeled as an
equivalent current dipole lying under the center of the pattern. The
orientation of the dipole is approximately perpendicular to the
central sulcus, suggesting that the source lies within the sulcus.
The best-fitting parameters for the dipole are given in Table 1.

We can relate the location of this central source to the
position of the central sulcus, which is well-established for one
subject (SW) by previous sensorimotor studies conducted in our
laboratory. Motor activity associated with voluntary ballistic
fle re of the left index finger was observed about 2 cm lower along
the sulcus, which places the central source near the eye area of the
sensorimotor sequence.

Studies with left and right visual field stimulation show that
response amplitudes for the central source are little changed,
indicating that the source has a different functional property than
that exhibited by the occipital sources in left and right
hemispheres. We note that the medial temporal area of the macaque
monkey (Van Essen et al. 1981) also contains representations of
ipsilateral and contralateral hemifields as does this one.

One hypothesis explaining this activity could be that it is associated with motor activity related to eye movements in tracking the velocity modulation of the grating. We argue that this is unlikely, since the eye is incapable of tracking oscillations as rapid as 7 Hz. More likely, this activity is in response to signals ultimately originating in the visual cortex that are provided to the eye motor area for comparison purposes (as suggested by von Holst and Mittelstaedt). This conjecture has some support in the preliminary observations for subject PL that there is a consistent increase in apparent latency on going from the occipital to central field patterns, and this suggests a causal relationship. Thus it appears that there is sequential activity, beginning in the occipital area and shifting to the central.

Table 1   Parameters for Model Dipole Sources (Subject: SW)

The declination angle θ is measured with respect to the polar axis extending from the center of the head to the vertex; the azimuthal angle ϕ is measured clockwise about the polar axis from the inion; and the angle ψ gives the orientation of the dipole moment, measured from the azimuthal plane counterclockwise about the radius to the dipole.

Source	θ (deg)	ϕ (deg)	ψ (deg)	d (cm)	Q (nA-m)
Right Occipital	90	6	125	2.0	6.0
Left Occipital	85	-15	260	2.0	6.0
Right Central	45	75	135	3.2	2.2

This study demonstrates that the piranha technique can be successfully applied in situations where the field from one source (in this case the pair of occipital sources) is fairly uniform in the area where the second source (central source) produces its strongest field.

ENDOGENEOUS LONG-LATENCY ACTIVITY

One of the main goals of this project is to identify and locate regions of the brain whose activity reflects the state of a human subject and differentiates among the degree and kinds of activity in which he is engaged. Our work in this area began with a project to detect the magnetic counterpart of the electrical P300 component. As there are more than one thousand papers in the literature related to this component, the wealth and consistency of the data stimulated considerable interest in its intracranial origin. Neuromagnetic studies in our laboratory revealed that the magnetic component, designated P300m, could be observed for a visual oddball task, and by identifying the positions over the scalp for the field extrema the procedure of Williamson and Kaufman (1981) could be used to locate the equivalent current dipole source in each hemisphere where activity was observed (Okada et al. 1983). In this same study maps were also obtained for an enhanced earlier component N200m observed in temporal and occipital areas. The sources of both N200m and P300m could be attributed to neural generators lying in or near the

hippocampal formation. The orientation of each equivalent dipole source was approximately rostral, so that the deduced sources of P300m and N200m contribute at least partially to P300 and N200 observed with scalp electrodes. Simultaneous measurements of P300 with an electrode at Pz relative to the mastoid displayed a similar waveform, supporting the notion of a common neural substrate.

This assignment of source location for P300m is consistent with depth electrode measurements of Halgren et al. (1980) at UCLA and McCarthy et al. (1982, 1985) at West Haven Veterans Hospital. They observed strong electrical activity near the hippocampal formation that coincides with P300 in their patients, although the waveforms of depth and scalp recordings did not coincide. In addition to identifying the origin of N200m and P300m, our magnetic study showed it is possible to detect magnetic activity of at least some subcortical regions lying deep within the brain.

Auditory P300m

Since the auditory P300 typically occurs about 100 msec prior to the visual P300, it is possible that it has a different source. Indeed, investigators have applied the label "P300" to peaks of diverse latencies as long as their distribution about the scalp was similar and showed similar reactions to experimental manipulations. While this attribution is plausible, there was no direct evidence that all of the peaks to which the label "P300" has been applied are

in fact manifestations of the activity of the same neural generator.

The most suggestive evidence that the sources of auditory and visual P300m differ is based on results obtained at UCLA by Jackson Beatty and his colleagues (personal communication) who reported a reversal of the polarity of late components of the event-related field (ERF) over auditory cortex. If this finding were confirmed it would mean that at least a portion of the auditory P300m, and by inference P300, is cortical rather than subcortical in origin.

To test this idea we implemented an experiment in which the subject anticipates whether a highly probable or highly improbable stimulus will appear on a forthcoming trial by depressing one of two buttons. Then the stimulus is presented with one of two possible outcomes, i.e., confirming the prediction or disconfirming it. We then analyzed responses for confirming frequent and infrequent stimuli and for disconfirming frequent and infrequent stimuli separately. All four types of responses were measured both electrically (between Pz and mastoid) as well as magnetically. The ERF's were measured at many places about the head by Sarah Curtis, a Graduate Research Assistant.

We have screened many subjects to obtain a subset of subjects that give large P300s. This makes it possible to map the ERFs with an optimal signal-to-noise ratio. We were unable to confirm the UCLA finding, since we observed no reversal of field direction over the

superior temporal lobe, nor over the entire temporal region of the
scalp. The data accumulated using both visual and auditory stimuli
display strong fields over the temporal area, but a reversal is seen
only for early components (N100m and P200m) appearing for both
frequent and infrequent stimuli. This is expected since these
components have already been identified by magnetic studies to arise
from sources in cr near primary auditory cortex (Hari et al. 1980;
Pelizzone et al. 1985). The later components that do not reverse
direction over the temporal lobe vary in amplitude with the
"surprisal" of the stimuli and have the same scalp distribution to
within the experimental uncertainty for both visual and auditory
events. Thus it appears that the sources of both visual and auditory
P300m are very close to each other, if they are not the same.

This experiment was preceded by other variants of the odd-ball
paradigm, but these were discarded because of the adaptation of the
subject to the surprise value of stimuli over the very large number
of trials needed to complete a field map.

Comparison of P300 and P300m

During the summer of 1984 a collaborative study was carried out
between members of our group at the Neuromagnetism Laboratory (NML)
and members of Professor Emmanual Donchin's group in the Cognitive
Psychophysiology Laboratory (CPL) of the University of Illinois. The
purpose was to investigate the similarity of sources of P300 that

differ in latency and waveform because of experimental
manipulations. The paradigm was a variant of the earlier study
conducted by McCarthy and Donchin (1981) and by Magliero et al.
(1984) at CPL who presented data that implies the latency of P300 is
largely affected by stimulus evaluation processes and is essentially
insensitive ot the time required for response selection and
execution. This conclusion was reached by having subjects determine
whether the word RIGHT or LEFT is embedded in a square matrix of
characters. The ease with which the word could be identified was
varied by introducing "noise" into the matrix in the form of letters
instead of crosses for the other elements of the matrix.
Furthermore, on some trials the subject was required to respond in a
manner incompatible with the stimulus (e.g., press a button with the
right hand when the command was LEFT). The subject's reaction time
increased when they were required to make incompatible responses.
The RT also increased when the command was difficult to detect.
Moreover, these two effects have proven to be additive. Given this
pattern of results it was significant that the latency of P300 was
found not to be affected by the need to respond incompatibly, but
was affected by the addition of noise to the matrix.

While the pattern of results was rather clear from these
earlier studies, and was well supported by subsequent work in CPL
and other laboratories (Ford et al. 1982), there lingers a problem.
The pattern of the ERP elicited by the noisy matrices was quite

different from the pattern elicited by the "clean" matrices. In the latter case the ERP contained a sharp, clear peak positivity. When noise was added to the matrix the waveform was characterized by a relatively slow wave with at least two peaks. McCarthy and Donchin interpreted the noise-elicited pattern as reflecting the shift in time by the P300. Analyses of the pattern of scalp distributions, as well as the data reported by Magliero et al. (1984) are consistent with this interpretation. It would however be very useful to determine in a more direct manner which of the components of the ERP elicited by noisy matrices is generated in the same sites from which the P300 is clearly elicited when the stimulus is not noisy. The neuromagnetic procedure offered the possibility of such a direct means for comparing the origin of components elicited across different conditions.

The goal of the experiment was to determine whether the stimuli used by McCarthy and Donchin can be used to obtain ERFs comparable to ERPs, including the deflections in the ERP waveform conventionally referred to as "P300". This cooperative effort between the CPL and NML was possible because of the availability of the PEARL system (Heffley et al. 1985), a portable data acquisition and experimental control system developed at the CPL in which the experimental paradigm described above was implemented. Since the neuromagnetic measurements could best be done with the multiple-sensor Freddy, the most effective means for accomplishing

this research was to transport PEARL to our laboratory.

Methods

Three subjects were run in the experiments, two 25 year old right-handed females participated in a visual oddball paradigm and one 26 year old right-handed male was run in a noise/no noise oddball paradigm. In the visual oddball the words LEFT and RIGHT were generated in a Bernoulli sequence with the presentation probability of 0.25 for the word LEFT. The words were displayed in the center of the screen with a visual angle that subtended approximately 2.5 deg. In the noise/no noise experiment the stimuli were generated according to the rules described by McCarthy and Donchin (1981).

Subjects were given practice in the experiment prior to the recording sessions. Subjects were instructed to count the word LEFT and report their total at the end of each experimental block. EEG and EOG electrodes were attached to the subject. The subject reclined on a table with the SQUID array of Freddy positioned within 1 cm of the subject's scalp. The visual stimuli were displayed on a Panasonic monitor placed sufficiently far from Freddy that no simulus artifact was produced by its magnetic field.

The neuromagnetic recording system consisted of the 5-channel sensing system, with the signal in each channel passing through a Rockland bandpass filter, a comb filter to remove residual signals

synchronized with the power line, and the electronic cancellation
network to reduce ambient field noise. Then the signal was passed to
the PEARL computer. EEG activity was recorded from Fz, Cz, and Pz
using a GRASS EEG amplifier. EOG activity was corrected off-line
(Gratton et al. 1983). The electrical and magnetic data were
recorded concurrently and the single trial data were written to
magnetic tape for subsequent analysis. This led to the computation
of five different average ERFs at the same time as we recorded the
average ERPs associated with the rare and frequent events. The field
measurements were replicated numerous times so that we could
generate field maps that would allow us to compute the location of
the source of the P300m, using a spherical model for the subject's
head (Williamson and Kaufman, 1981). In this experiment the field
was measured at 45 positions over the right temporal region, 80
positions over the occipital region, and 90 positions over the left
temporal region. Since most of these positions were non-overlapping,
the field was measured at approximately 215 distinct locations for
subject SG. The coordinate system used for placing the sensor was
referred to the ear canal or to the inion. When measuring the field
in the temporal region the horizontal axis was the line joining the
ear canal to the outer canthus of the eye. When measuring the field
over the occipital regions the horizontal axis passed through the
inion and was parallel to the horizontal axis for the temporal
region, with the midline as the vertical axis.

The outputs of the signal channels and the reference channels were bandpass filtered between 0.3 and 45 Hz before signal averaging. The output of the Pz channel was collected both with and without Rockland filtering. Whenever noise levels exceeded a value that resulted in signal saturation, the epoch in which the event occurred was eliminated from subsequent analysis.

In these first studies we encountered difficulties using the Rockland filters. The low-frequency cutoff distorted the waveforms of the responses so that the "P300m" deflection is shifted in time and distorted in shape. This arose from two effects. The first was a non-linear delay for different frequencies. For example, a 1 Hz sine wave was delayed by 280 msec, while a 5 Hz sine wave was delayed by 100 msec. This had the effect of differentially shifting components of the ERF. The second distortion was created when the input to the Rockland was overloaded, causing the filters to "ring". When such epochs were included in the average of the waveform it was difficult to identify any ERF components.

The electrical activity recorded at the parietal electrode was filtered in two different ways before averaging. The electrical activity was filtered with an 8 sec time constant and a high frequency cutoff of 35 Hz, with roll-offs of 3 dB per octave. This resulted in minimal distortion of the average waveform. The same activity was also averaged after being processed by the Rockland filters (bandwidth of 0.3-45 Hz and roll-offs of 48 dB per octave)

for comparison with the ERFs.

Two dominant components appear in the ERP waveforms. One is a large positivity occurring aroung 250-300 msec, maximal at Pz, which is present in both the rare and frequent plots. This component is labeled P200. The second component is a larger positivity occurring around 450 msec, maximal at Pz, which is present only for rare stimuli. Based on scalp distribution, latency, and sensitivity to experimental manipulation, we label this component P300. It was not easy, though not impossible, to identify the P300 component with some confidence after the data had been passed through the Rockland filters. Similar waveforms were observed in the magnetic records.

Comparison of the waveforms across a session reveals that the amplitudes of the P300 and P300m components decrease dramatically. This is what one might expect if the oddball task had become automated during the course of the recording session. Alternatively, the effect could be due to fatigue, boredom, or motivational changes. The inconsistency across recording sessions adds yet another caveat in the interpretation of the data.

Polarity reveral of the P300m waveform was observed for measurements over occipital and temporal regions of a given hemisphere. The scalp distribution of amplitude was qualitatively quite similar to those reported by Okada et al. (1983) obtained using visual gratings as stimuli. Despite the problems encountered

with the Rockland filters, the data for one of the subjects (SG) in the visual oddball paradigm were analyzed and isofield contour maps were generated. This indicated that the field extrema in the occipital region of left and right hemispheres were not well defined. This is likely due to overlap of opposing fields from sources in the left and right hemispheres. However, the location of he extremum to the right of the midline could be estimated by interpolation. Associating this occipital extremum with the extremum of opposite polarity over the right temporal region, the location of the underlying equivalent current dipole source could be estimated. Despite the evident "noisiness" of the data, it was apparent that the source is very deep within the brain. The equivalent dipole appears to be located within 1 cm of the position of the source in the earlier experiment using grating stimuli. This places the source in or near the hippocampal formaiton as concluded previously. It should be stressed that this consistency in source location is present despite the fact that alphanumeric stimuli were employed in this experiment, while grating stimuli were employed in the earlier experiment.

It is worth noting that students of the limbic system are unclear about the precise boundaries of the so-called hippocampal formation. It is not a well-defined anatomical entity. Even so, our results are consistent with the previous results, and as Halgren and his colleagues have pointed out, strongly implicate the limbic

system.

The preceding experiment was conducted to determine if
alphanumeric stimuli can be used effectively to conduct magnetic
P300m studies. An important criterion is whether or not the
signal-to-noise ratio is adqueate to permit distinctions among
sources that differ in location. It is clear that this is possible,
if and only if the sources are in widely separated places, as
difficulties in data quality do exist.

Visual Noise Experiment

Our main goal is still to replicate the McCarthy and Donchin
experiment and deterine if the change in P300m due to the addition
of visual noise is due to a change in the source of the response or
if it is due instead to a modulation in activity of the same source
of P300m. Unfortunately the PEARL system had to be moved from NML,
since we had run out of the time allocated for it. We are presently
completing the programming effort to develop the software necessary
for our computers to replace PEARL. Since most of the logistical
problems involved in the CPL-NML collaboration have been solved, it
makes sense to continue this effort once the programs are ready.
Both groups are quite eager to continue the collaboration, and
proposals to this effect are being considered.

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Joint Colloquium for the Departments of Physics and Psychology, New York University, 18 February 1982.

Colloquium, Physics Department, University of Toronto, Toronto, Canada, 26 February 1982.

Colloquium, Physics Department, Dalhousie University, Halifax, Canada, 7 April 1982.

Colloquium, Physics Department, City College of City University of New York, 28 April 1982.

Research Seminar, Laboratorio di Elltronica della Stato Solido, CNR, Rome, Italy, 2 May 1982.

General Physics Colloquium, A.T.T. Bell Laboratories, Murray Hill, New Jersey, 25 May 1982.

Invited Plenary Talk, 1982 Applied Superconductivity Conference, Knoxville, Tennessee, 2 December 1982.

Colloquium, Department of Psychology, UCLA, Los Angeles, California, 22 January 1983.

Colloquium, Physics Department, Dartmouth College, Hanover, New Hampshire, 11 February 1983.

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Colloquium, Department of Psychology, University of Illinois, 14 April 1983.

Physical Science Colloquium, I.B.M. Watson Research Center, Yorktown Heights, New York, 10 May 1983.

Seminar, Office of Naval Research, Arlington, Virginia, 16 June
1983.

Seminar, Jet Propulsion Laboratory, California Institute of
Technology, Pasadena, California, 14 October 1983.

Invited Review on NYU Work, Meeting of CHABA Committee on Hearing,
Bioacoustics, and Biomechanics, National Academy of Sciences,
Washington, DC, 21 October 1983.

Colloquium, Francis Bitter National Magnet Laboratory, M.I.T.,
Cambridge, Massachusetts, 31 October 1983.

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22 November 1983.

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Massachusetts, 27 February 1984.

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Physics, University of Wisconsin, Madison, Wisconsin, 30 March
1984.

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Institute of Technology and New Jersey University of Medicine
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Mexico 25 April 1984.

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Alamos, New Mexico, 26 April 1984.

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Riverside, California, 30 April 1984.

Research Seminar, Review of Air Force Sponsored Basic Research in
Visual Information Processing, Sarasota, Florida, 6 May 1984.

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Engineering, Otaniemi, Finland, 1 August 1984.

Evening Public Lecture, at the 5th World Conference on Biomagnetism, Vancouver, Canada, 27 August 1984.

Seminar, Physics Department, University of British Columbia, Vancouver, Canada, 29 August 1983.

Colloquium, Department of Psychology, State University of New York at Stony Brook, 16 October 1984.

Invited Lecture, The New York Hospital - Cornell Medical Center, Department of Neurology, Division of Cognitive Neuroscience, 17 October 1984.

Invited talk, Electronic Reduction of Ambient Noise Pickup with a Biomagnetic SQUID Array," SQUID Magnetometry Workshop, Coolfont, Berkeley Springs, West Virginia, 11 November 1984.

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Evening Lecture, Institute for Amorphous Studies, Bloomfield Hills, Michigan, 6 December 1984.

Colloquium, Physics Department, Brooklyn College, New York, 10 December 1984.

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from Evoked Potentials
Volume 3 "Frontiers of Clinical Neuroscience
Edited by:
Roger Q. Cracco
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CHAPTER NINE

The Neuromagnetic Field

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In 1963. Gerhard Baule and Richard McFee (3) discovered that a magnetic field associated with the flow of electric current in the heart could be detected outside the chest of a human subject. This weak field was capable of inducing a detectable electric voltage in a 2.000.000-turn coil of copper wire wound about a magnetic core. Because the field was so weak. the experiment had to be conducted with the subject lying in the middle of a pasture, far from power lines and equipment that might interfere with the measurement.

This pioneering experiment was the first of many studies by other investigators and ultimately led to the founding of a new field of scientific research. which has come to be called biomagnetism. Workers in this area study magnetic fields produced by organs of the body or by magnetic contaminants of the body. This paper describes a major subdivision of biomagnetism. namely neuromagnetism. which is the study of magnetic fields associated with the flow of ionic currents in the nervous system.

It is well known that electric and magnetic phenomena are intimately related to each other. In that a magnetic field is always associated with moving charges (electric current), it follows that the flow of ionic current in neural tissue must also generate magnetic fields. One of Maxwell's equations (which is based in part on the work of two early nineteenth century French scientists. Jean Baptiste Biot and Felix Savart) allows us to predict the direction and strength of the magnetic field whenever a charge is moved through space. For example.

an electric current flowing within the elongated dendrite of a pyramidal cell is accompanied by a magnetic field in its surrounding space. The field encircles the dendrite and. seen from one end. is directed counterclockwise if current is flowing toward the observer and clockwise if it is flowing away. In the case of currents flowing in many dendrites at the same time. the field everywhere in space can be computed by summing (integrating) the contributions of the fields of each infinitesimal element of the flowing current. This is also true when determining the field associated with current flowing in three-dimensional conducting volumes. in sheets (e.g.. the dermis of the scalp). and in complex circuits of neurons. In fact. the pattern and strength of the magnetic field is due to the density of current and the direction and speed of its flow within each element of the conducting fiber. sheet. or volume. We shall see that the applicability of these simple physical facts to electrically active biological tissues allows us to make some very general statements about the sources of fields observed external to the human scalp.

The magnetic field associated with the flow of current in the fiber segment of Figure 9.1 is described by the circular lines surrounding the fiber. There is no magnetic field directed radially outward from the fiber. Lines of magnetic field. indicated by the symbol B. are continuous—they have no beginning or end. The strength of the field measured at a point very close to the fiber. where the fiber can then be considered infinitely long. is inversely proportional to the distance between the point and the fiber. This follows from Ampere's rule. which holds that the field integrated along a circular path centered on the fiber is propor-
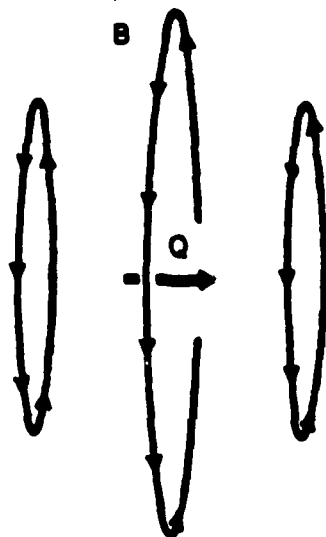
Figure 9.1. A current-carrying fiber is encircled by a magnetic field (B).

tional to the enclosed current regardless of the diameter of the path.

We can think of a large conducting sheet. e.g.. the skin to which we attach electrodes in measuring the EEG. as composed of an infinite set of very thin parallel fibers. with each carrying the same amount of current and having its own magnetic field. Superimposing all these fields produces a net field that is wholly parallel to the surfaces of the skin and oriented at a right angle to the current. There is no component of the field normal to the sheet.

This distinction between the fields associated with flow of current in a dendrite and the flow of current in a flat surface like the skin enables us to visualize why it is possible to measure fields from neurons while discriminating against fields from volume currents flowing in intervening tissues. As is shown in Figure 9.2. the field leaving and entering the surface of the skin is due to the flow of ionic current in a hypothetical dendrite. The currents that flow in the dermis to produce potential differences between points on the skin do not contribute to the normal component of the field but do contribute to the field tangential to the skin. A sensor designed to pick up the field normal to the skin will be insensitive to the tangential field.

It is of further significance that steady or slowly changing magnetic fields are not appreciably affected by the presence of biological tissues. Hence the field produced by a current-carrying fiber contained within the human body will be essentially the same when measured outside the body as it would be were there no body enclosing the fiber. This "transparency" of the human body to magnetic fields is one of the most important reasons for interest in neuromagnetism.

Let us now consider a neuron with an elongated dendrite. a cell body, and an axon. Depolarization of the membrane at the end of the dendrite by a neurotransmitter causes a current of potassium and sodium ions to flow within the dendrite toward the cell body. This current can be represented by an arrow pointing in the direction of the current within the dendrite. and it results in an imbalance in charge between the point of depolarization at the distal end of the dendrite and other points along its length. The accompanying electric field produces a flow of ionic current in the conducting volume surrounding the dendrite. This "volume current" flows in the direction opposite to the intracellular current.

Based on the principles described above. one would predict the presence of a magnetic field around the dendrite owing to the flow of current within its length. as in the case of any conducting fiber. Moreover. this field would be totally unaffected by the surrounding material. Also. the strength of the field some distance away from the comparatively short dendrite decreases more rapidly with distance than does the field associated with current flow in a long fiber. viz. the field strength would be inversely proportional to the square of that distance. A magnetic field is also associated with each region of the volume current set up by the difference in charge density along the length of the dendrite. However. in a uniform. homogeneous conducting medium. there is a complete cancellation of the contributions from all the regions in the surrounding space. As a result of this net cancellation. the field associated with depolarization (or hyperpolarization) of the neuron is due to the axial intracellular current alone.

Physiologists make use of the concept of current dipole as a building block in constructing

models of more complicated distributions of current in biological tissues. In fact, distributions of volume currents and of potential differences measured within and outside conducting volumes are often "explained" as resulting from the presence of one or more underlying current dipoles. When the sources of observed currents, potentials, or magnetic fields are deduced from measurements of these phenomena, it is common to refer to an "equivalent current dipole." This is shorthand for the notion that the actual source could be a number of simultaneously active neurons confined to a small region of active neural tissue, but their net effect can be accounted for by assuming that the source is a single infinitesimal current dipole. This assumption is justified by the fact that the empirically measured field pattern approximates that which would be produced by a current dipole.

Many cells of the brain have dendritic trees that cannot be described as simple current dipoles: their many branches have no average preferred direction, and current flows within them in all directions at once. Hence the fields associated with current flowing in these branches would largely or completely offset each other (cancel) some distance away. However, the apical dendrites of pyramidal cells of the cortex do have a preferred alignment normal to the surface of the brain, and might well be the major sources of observed fields normal to the scalp.

The neural impulse (action potential) occurs when the membrane of a neuron is sufficiently depolarized by an incoming signal (e.g., by an excitatory postsynaptic potential elicited by a neurotransmitter). This initiates a flow of sodium ions across the membrane into the cell, which depolarizes the membrane. The electric field associated with this build-up of positive charge produces a flow of current within the length of the axon in the direction of travel of the "depolarization" front of the impulse. As the membrane continues to respond to the excitation, a "repolarization" phase develops, with an axial intracellular flow in the opposite direction and potassium ions flowing outward through the membrane. We shall not go into the details of this process, which involves the transport of several species of ions across the membrane and along the length of the axon as
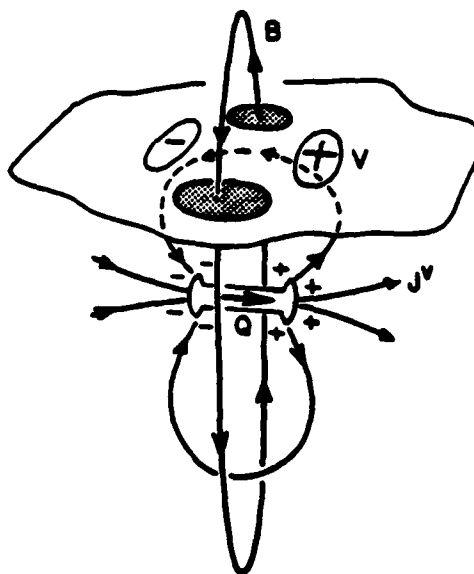

Figure 9.2. Magnetic field (B) associated with hypothetical dendrite of dipole moment (Q) immersed in a conducting volume. Volume currents (J^v) do not contribute to the field normal to the skin but are associated with the scalp potential (V).

well as in the electrolyte in which the axon is normally bathed. For our purposes it is sufficient to note that the action potential can be modelled as two closely spaced current dipoles of opposite orientation within the axon that travel in the same direction. These two current dipoles are a special case of a "current quadrupole." Because the fields of both current segments are opposed in direction, the field strength falls off much more rapidly with distance from the axon than does that of a dipole. In fact, the flux density is inversely proportional to the cube of the distance between a field sensor and the axon. However, as John Wikswo and his colleagues (17-19) have shown, it is possible to measure the field at a point near the surface of the axon and observe the reversal in its direction when the current representing the depolarization front is replaced by that representing the repolarization process as the action potential passes the sensor (see Fig. 9.3).
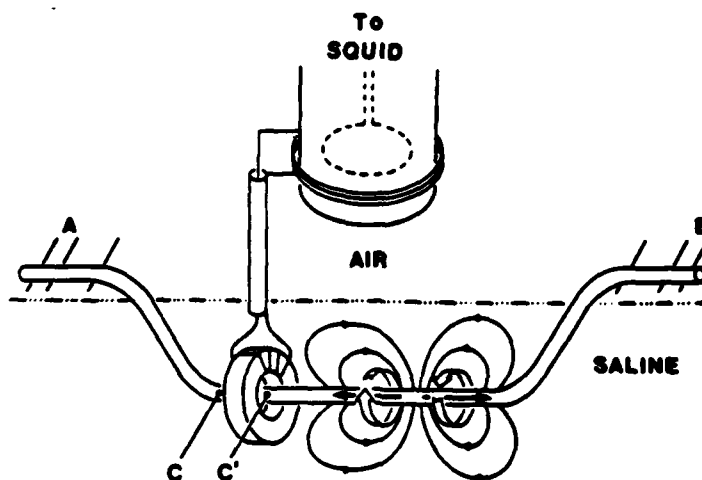
Figure 9.3. Measuring the field associated with an action potential as it travels along the length of an axon.

Such measurements can be made from single axon and from a bundle of axons (a nerve) when the action potentials in each axon are more or less in synchrony. However, if the action potentials in the individual axons comprising the nerve are out of step with each other, the fields due to the repolarization currents would tend to cancel those due to the depolarization front. It is unlikely that the individual action potentials in axons of a large population of cells in the brain would be in step with each other, and therefore they should contribute very little to the field observed external to the scalp.

By contrast, subthreshold depolarization of one end of a dendrite is not sufficient to initiate an action potential, but it does result in a graded potential that travels diffusely along its length. Even if there is some asynchrony of such events, the fields associated with such axial current flow in dendrites would not cancel each other because of its slowly graded and unidirectional character; i.e., there is no abrupt reversal of direction of current dipoles over time as in the impulse. Hence, fields arising from a mass of cortical tissue are most likely to result from current flow associated with graded activity in elongated dendrites.

As is indicated above, currents flowing in the dermis of the scalp as a result of neural activity give rise to the conventional EEG. These skin currents are of extremely low density and, therefore, must have very weak fields. What is more, the field due to broad areas of current flowing within and parallel to the surface of the skin would always be parallel to the scalp. As was already indicated, this type of current would make no contribution to the field normal to the scalp. These inferences are solidly supported by the empirical finding that the currents associated with fields observed to be normal to the scalp are opposite in direction to the currents that give rise to observed potential differences on the scalp (cf. 10). Therefore, scalp currents cannot be major contributors to the field normal to the scalp. It should be noted that precisely the same arguments apply to current flowing in other membranes and conducting media between the skull and the brain. Hence the predominant source of the external field is the intracellular flow of current in elongated dendrites of the cells of the brain.

This, in rough form, is a summary of all the arguments for an intracellular neural origin for magnetic fields that emerge from and reenter the scalp. It justifies employing the current dipole as a model for the net current flowing in a concentrated population of active neurons when its neuromagnetic field is measured at a distance that is large relative to the size of the

active group of neurons. Empirical support for this assertion is provided below. However. before describing actual measures of such fields. it is important to be clear about some of the ways in which the field of a current dipole, as well as the potential differences it produces. are affected by its physical milieu.

As in other types of physiological measurements. the current dipole is a widely used model of sources of sensory evoked potentials (EPs) measured at the scalp. EPs are time-locked *to sensory* stimuli, and it is accepted that the stimuli evoke neural activity that results in the spread of *volume currents* throughout the intracranial space. through and around the skull, and into the skin. With many electrodes attached to the scalp. it is possible to determine how the potentials vary in direction and strength relative to some more distant electrode. The resulting map of potentials allows one to make inferences about the location of their source (usually modelled as a current dipole) in the brain. However. owing to the smearing effects of intervening tissues, fluids, and bone. the inferences may be quite inaccurate. To make them more accurate. we need a *more realistic notion of the ways in which local anisotropies of conductivity affect the volume currents before they reach the scalp.* By contrast. as was stated above, these same tissues and fluids have no effect on the slowly changing (< 1.000 Hz) magnetic field normal to the scalp. Consequently. it is possible to make reasonable inferences as to the locations of sources using a model of the head that ignores effects of intervening tissues, although these effects cannot be ignored in working with electric potential data.

One instructive model, illustrated in Figure 9.4A. is that of a current dipole *immersed in a* conducting volume within a semiinfinite half-space. The dipole is viewed from above the surface of the half-space. The upper boundary of the half-space separates the conducting volume from air. The current dipole is oriented parallel to the upper boundary. and its magnetic field emerges from one region and reenters the half-space in another region of the surface of the boundary. The contour lines on the surface of the boundary represent equal *field-strength lines (isofield contours). and the* field is at a maximum in the center of each set of contours. These contour lines are "dipolar"

in character in the sense that an actual single equivalent current dipole would produce this *same set of contours even if their actual source* was some population of neurons. Now. were the dipole rotated through 90° to be oriented normal to the surface, there would be no detectable field outside the half-space. However. were the dipole tilted so that it was at some intermediate angle. then it can be decomposed into a component parallel to the surface and a component normal to the surface. In this case. the external field would be determined exclusively by the parallel component with no contribution from the normal component.

This should be contrasted with the distribution of potentials produced on *the surface of* the half-space by the volume currents associated with the current dipole. which is also illustrated in Figure 9.4B. With the dipole parallel to the surface. the isopotential contours resemble those of the isofield contours but are rotated through 90° on the surface. However. when the dipole is tilted, its normal component contributes to the pattern of potentials. causing it to lose its symmetry. As a matter of fact. were the dipole oriented at 90° relative to the surface ($O = 0°$). its volume currents would produce a unipolar plot of concentric circles directly overhead. Now. were uniform layers of different conductivity placed between the current dipole and the surface. they would tend to spread the distribution of potentials but would have no effect on the distribution of the magnetic field normal to the surface.

This particular model is of more than didactic value. If we model a source of brain activity as a current dipole located in the cortex but close to the skull. then the curvature of the skull could be ignored and the half-space model used to compute the location of the source. In fact. the dipole would be positioned between the two field extrema (the maximum fields directed outward and inward relative to the surface). and its depth would be the separation between these extrema divided by the square root of two (20). In the case of a tilted dipole. its component parallel to the surface can be localized in precisely the same way. However. in the case of potential measurements. unless we had *a priori* knowledge of the orientation of the current dipole. owing to the resulting asymmetry of the pattern of potentials it would
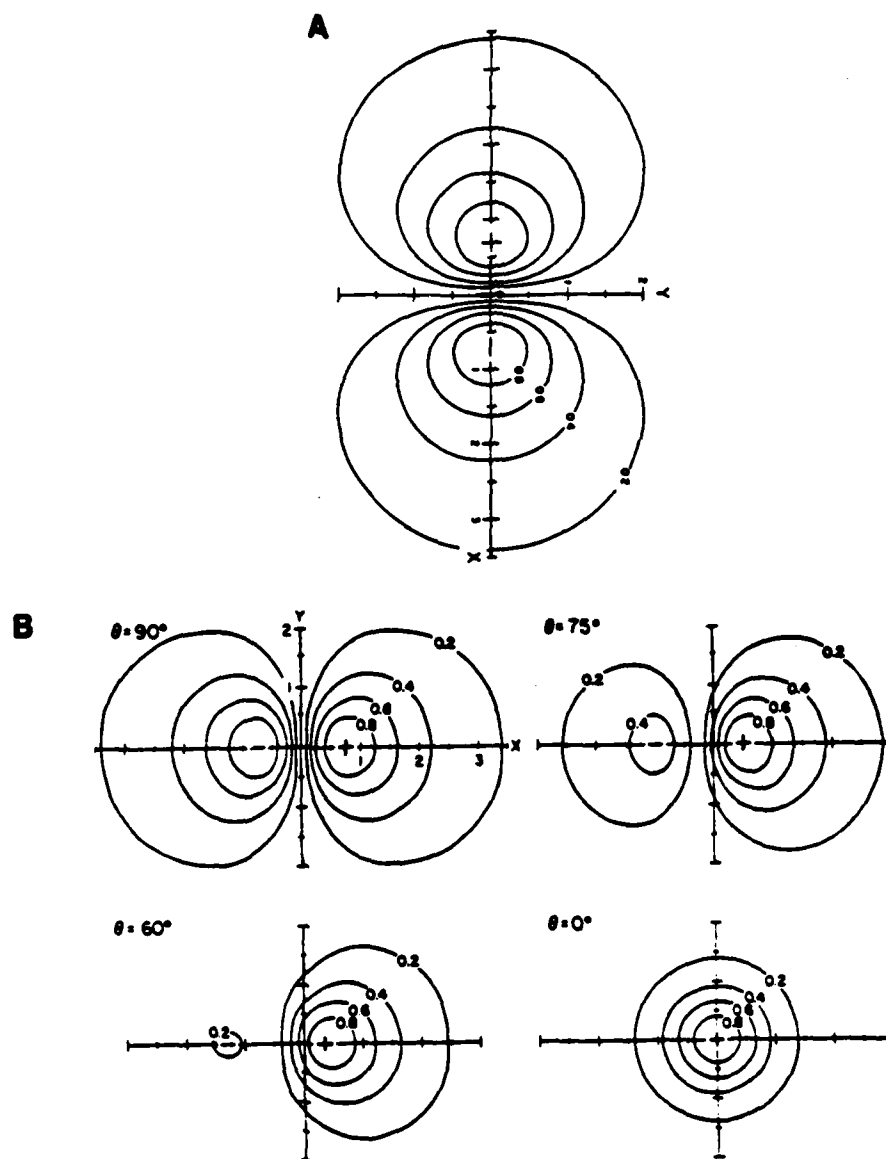
A

B

Figure 9.4.   (A) Field pattern (isofield contours) associated with a current dipole in a semi-infinite half-space. (B) Isopotential contours associated with a current dipole having different orientation in the same half-space.

be more difficult to compute the location of the source of the potentials in that a large number of precise measurements would be needed. and these would have to be fitted to an appropriately complicated model. Thus. even when many electrodes are used to obtain isopotential contours. we must still deal with the problems of the spreading of volume currents because of variations in conductivity within the head and their possible asymmetry. In addition. there is no way to distinguish the potentials produced by a tangential current dipole and those associated with two adjacent and radially oriented dipoles of opposite polarity.

Of much greater significance than the relative simplicity of locating a dipolar source is the difference in the abilities of the two measures to resolve simultaneously active though spatially separated sources. The superposition principle applies to both fields and volume currents. The distribution of fields or potentials at the surface when two dipolar sources are active is the same as the sum of their distributions when they are active separately. The strength of the magnetic field of a current dipole falls off with the square of the distance between the source and the sensor. In contrast. the magnitudes of sensed potentials depend on the spacing of electrodes on the scalp. because we always measure potentials between electrodes or between sets of electrodes; i.e.. there is always a reference for a potential measurement. and the amplitude of the measured potential depends on the reference as well as on the strength of the source and the effects of intervening media on the volume currents. This could make it extremely difficult to resolve separate sources. However. the magnetic field sensor is essentially unipolar and there is no need for a reference electrode. as there is in measuring the EEG. Therefore. the field sensor reacts most strongly to the nearer source. and. by moving it about the surface to map the field. it is possible to resolve sources that are separated by remarkably small distances. a capability that has rarely been demonstrated with electrodes attached to the surface of the scalp.

When the current dipole is distant from the surface. then the curvature of the surface must be taken into account. Models that attempt to do this assume that the head can be represented by a sphere filled with a conducting solution.

To "explain" the distribution of potentials on the surface of a sphere. the radial variations in conductivity imposed by concentric layers of different conductivity must be taken into account. In that these layers have no effect on the normal component of the magnetic field external to the sphere. they can be ignored (8). Therefore. a very simple spherical model of the head suffices for locating and resolving sources of fields that are detected normal to the scalp.

One problem we have not mentioned is that of detecting very weak fields. In fact. external fields associated with neural currents can have magnitudes approaching one billionth the strength of the earth's steady field. The detection of such weak fields became possible when a cryogenic sensor. the superconducting quantum interference device (SQUID). was applied to measuring the field of the heart (6). This was done in a magnetically shielded room designed so that its interior would be relatively free of any ambient magnetic field. which would otherwise have interfered with their measurements.

Fields that arise from distant sources are relatively uniform in their spatial distribution. whereas those arising from nearby sources are nonuniform at the instrument. i.e.. have high spatial derivatives. It is possible to capitalize on this difference in fields by rejecting those that come from distant sources such as elevators. electronic instruments. and subway trains while detecting fields that arise from ionic current flow in the brain of a person whose head is held near the sensing instrument. To accomplish this. Brenner. Williamson. and Kaufman (5) used a SQUID together with a superconducting sensing coil known as a *second-order gradiometer*. which is illustrated in Figure 9.5.

This detection coil makes a differential measurement of the field between a position close to the head and another position a few centimeters farther away and is therefore relatively insensitive to fields from distant sources. which are generally uniform in space. Because fields from distant sources may have uniform spatial gradients. the gradiometer is designed so that the differential effect of the gradient on two of the coils is equal and opposite to the effect on the other two coils. This approach has proven to be adequate for a wide range of neuromagnetic measurements. even in an urban environ-
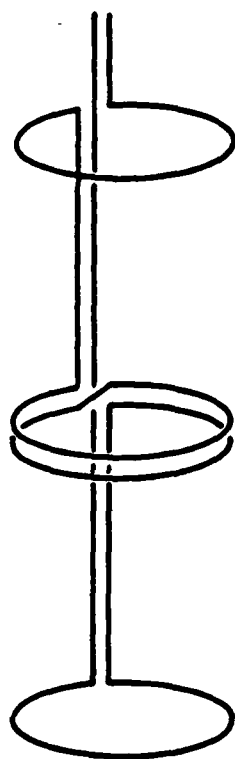
Figure 9.5. Schematic of second-order gradiometer.

ment where there are many sources of ambient field noise.

As is shown in Figure 9.6. the SQUID. gradiometer detection coil. and some electronic components of the superconducting sensing system are enclosed in a common container (a cryogenic dewar). where they are kept at the temperature of liquid helium. The dewar is placed in a holder that allows the experimenter to move it so that its tail section can be placed at various positions close to the subject's head. In most of our experiments. the subject reclines on a comfortable table and receives either visual. auditory. or somatic stimuli. We shall now describe some of the results obtained with this procedure and compare them with other similar measures.

In one experiment (10). we examined the response of the somatosensory cortex to a weak electrical stimulus applied to the median nerve

in the wrist. This particular somatosensory evoked response had been extensively studied in other laboratories either by measuring potential differences between electrodes at various positions on the scalp or by recording potentials between electrodes applied to the exposed surface of the brain. Apart from this rich set of data with which to compare our results. this particular response was well suited for magnetic studies in that the cortical tissue involved is known to include large numbers of neurons in the posterior bank of the central sulcus (the Rolandic fissure). and they are likely to be predominantly tangential to the scalp.

Brief electrical pulses were applied to the wrist at intervals of about 500 msec. The pickup coil of the gradiometer was centered near the central sulcus. and the SQUID output was applied to a computer for signal averaging. This was done repeatedly at many positions alongside and across the central sulcus. We observed a reversal of the polarity of the neuromagnetic field. which indicated that the equivalent current dipole representing the neurons activated by the stimulus is about 12 cm above the ear canal of this subject and approximately in line with the projection of the central sulcus onto the skull. Typical data are shown in Figure 9.7.

Maps of the evoked fields revealed the locations of the field extrema. i.e., the regions on the scalp where the flux density was at a maximum where the field emerged from and reentered the scalp. This enabled us to compute the depth of the source. which was about half way down the extent of the typical central sulcus (about 2 cm below the scalp). Moreover. the wave form of the response had a striking similarity to the shape of the same response recorded by an electrode on the surface of the exposed brain. as observed by Goff et al. (7) in patients undergoing brain surgery. Such a similarity is usually lacking in typical evoked potentials recorded between electrodes attached to the scalp. Moreover. no significant neuromagnetic response could be detected over the primary cortex ipsilateral to the stimulated wrist. By contrast. our potential measurements and those of other investigators indicate that many of the components of the evoked potential can be detected all over the scalp. including the side of the head ipsilateral to the wrist being stimulated. Such recordings could only
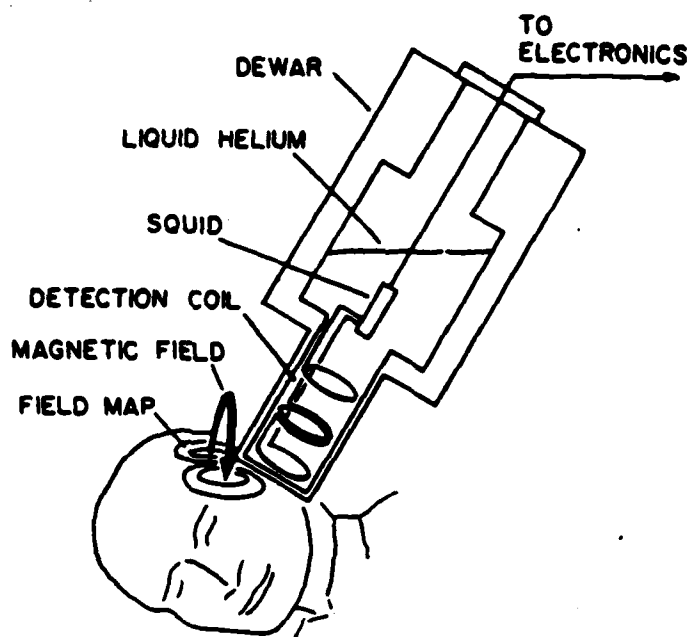
Figure 9.6. Schematic of gradiometer and SQUID immersed in liquid helium in a cryogenic dewar.

result from the widespread volume currents that underlie the evoked potential. The fact that responses could not be detected on the ipsilateral side indicates that the magnetic field is not due primarily to the volume currents but to the activity of the underlying neural tissue. This conclusion is reinforced by the fact that the direction of current flow that produces salient components of the evoked field is opposite to the direction of current flow that underlies correlated components of the evoked potential recorded from the exposed brain. In all cases that we have studied, the current source of the detected field flows in opposition to the current source of scalp-recorded EP. In that the latter phenomena are due to volume currents, the neuromagnetic field must be due to intracellular current flow.

The somatosensory pathways become active when the fingers are moved because of excitation of proprioceptors in the joints and muscles. However, the motor cortex, which is anterior to the somatosensory cortex on the opposite bank of the central sulcus, should become active prior to voluntary flexion of a finger. Okada, Williamson, and Kaufman (13) studied fields associated with activity of the motor cortex and of the subsequent activity of the somatosensory cortex associated with movement of the index finger.

The subject in this experiment was asked to flex the index finger of his left hand whenever a pattern appeared on a video display. This was repeated many times. Each time this was done, the pick-up coil of the gradiometer was at a different location over his scalp. Electrodes were placed on his forearm to detect the actual onset of flexion of his finger. This onset was used as a point of reference in time so that we could identify brain activity that preceded overt movement of the finger as well as the activity that accompanied and followed the movement. Activity of the cortex prior to flexion must indicate the initiation of motor action by the brain, whereas activity during and after flexion must indicate the proprioceptive feedback from the muscles and joint receptors. In fact, beginning about 40 or 50 msec prior to flexion the field outside the head could be attributed to a source in the anterior bank of the
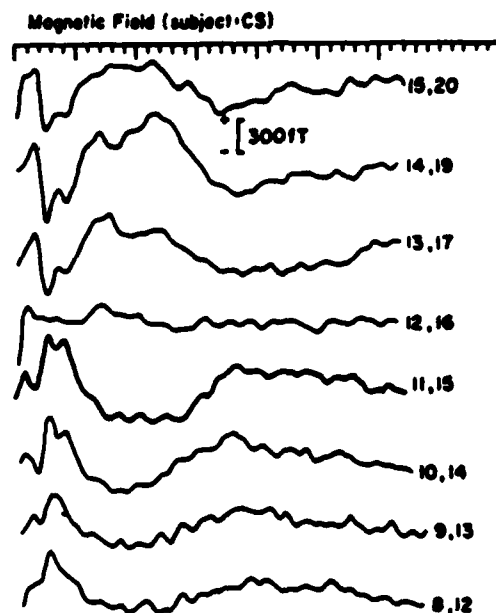
Magnetic Field (subject·CS)

Figure 9.7. Typical somatosensory evoked fields resulting from electrical stimulation of the median nerve. The lefthand number on the right side of each tracing is the distance between the pick-up coil and the ear canal (in cm), while the righthand number is the distance behind the nasion on the midline.

central sulcus (the motor cortex), whereas the field occurring during overt motion was owing to a more posterior source—in the somatosensory cortex. To verify this conclusion, we had the subject keep the index finger of his left hand relaxed while he used his other hand to bend the finger. It was assumed that this would result in activity of the somatosensory cortex, because the stretch and joint receptors in the left index finger would be stimulated. However, because the right hand was used to bend the finger, we predicted that the right hemisphere's motor cortex would not be active prior to this passive flexion of a finger on the left hand. These predictions were confirmed in that there was no detectable field over the right hemisphere prior to the onset of finger motion, but a field was detected during and after flexion. Thus it is possible to resolve activity of the motor cortex and that of the somatosensory cortex even though these are on opposite banks of the same sulcus in the brain.

Romani, Williamson, and Kaufman (15) set out to characterize sources of fields within the auditory cortex of the brain. The primary auditory projection area is located in the cortex within the lateral sulcus of the brain. Because it is generally true that neurons of the cortex are arranged in columns that are approximately normal to the surface of the cortex, those neurons lying within a sulcus should be largely tangential to the surface of the scalp, thus making them ideal candidates as sources of externally detectable neuromagnetic fields. It is also known that some areas of the auditory cortex in animals such as the cat and monkey are organized so that neurons sensitive to different bands of acoustic frequencies are located in different places. This is referred to as a "tonotopic" organization, and although such an organization is widely assumed to exist in man, there was no direct evidence that it actually exists, nor was there any evidence concerning its particular organization, which does vary among species of animals.

In our experiment, we utilized acoustic stimuli of different frequencies, e.g., 200, 600, 2,000, and 5,000 Hz. Each of these pure tones
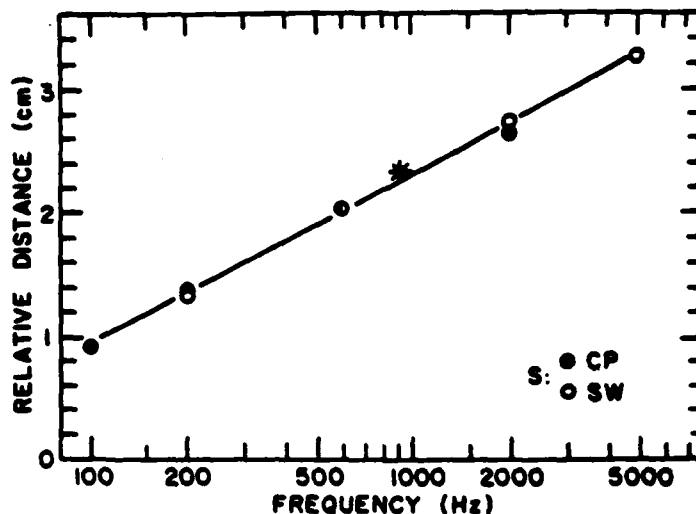
Figure 9.8. Log-linear relation between relative source position along the floor of the lateral sulcus and the carrier frequencies of acoustic stimuli.

was amplitude modulated at 32 Hz. These modulated tones were presented by earphones in a random order several times with the pick-up coil of the gradiometer placed at one of many different positions about one side of the head. The neuromagnetic field that was time-locked to the modulation frequency of each tone was detected. After collecting all the data. the responses were sorted according to the tones that were modulated. i.e.. the carrier frequencies. and these were used to plot the pattern of the field normal to the scalp associated with each of the tones. Analysis of these data revealed that the tones had separate sources, and these grew progressively deeper within the lateral sulcus with increasing frequency. In fact, there was a precise linear relationship between the logarithm of the carrier frequency and the cumulative distance from one source to another along the cortex within the sulcus (Fig. 9.8). This tonotopic map bears a striking similarity to the log-linear relationship between frequency and position along the basilar membrane of the inner ear in humans. It indicates that equal numbers of neurons are dedicated to each octave of the acoustic spectrum that was studied. Moreover. based on a few simple and

straightforward assumptions. we determined that the total ionic current (the total "current dipole moment") was the same for each of the tones. which is consistent with the above mentioned conclusion. Our calculations indicate that no more than about 50.000 neurons contribute to the field evoked by each of our stimuli. This is consistent with our finding that the sources we resolved are separated from each other by about only 4 mm per octave along the cortex. Although we have focussed on our own work in this area. it should be mentioned that other research groups have utilized the neuromagnetic method to study hemispheric asymmetries in response to acoustic stimuli and their possible relation to different functions of the two hemispheres.

In addition to studies of the somatic. motor. and auditory evoked fields. we also conducted a number of studies on the visual system. Although this is an area in which we have great interest and are continuing to do extensive work. space does not permit us to do more than touch on some of our most salient findings.

Breitmeyer (4) had human subjects release a button as soon as they were able to detect a pattern that was presented briefly on a screen.

This enabled him to measure the simple reaction time, which was much longer if the pattern was composed of many fine alternating light and dark bars than it was when a coarser pattern composed of fewer bars on the same screen was the stimulus. In fact, there was a monotonic increase in reaction time with the fineness of the pattern.

It is common to refer to patterns such as those used by Breitmeyer as differing in "spatial frequency": the patterns are produced by sinusoidally modulating the luminance in one dimension across the screen. (One reason for present widespread interest in such stimuli is the now widely accepted notion that the visual system can be described as one that does a crude kind of spatial Fourier analysis of patterns. This property of the visual system can be compared with the similar property of the auditory system.)

Brenner, Williamson, and Kaufman (5) used stimuli that were nearly identical to those employed in Breitmeyer's experiment. However, rather than measure reaction time, we measured the latency of the response of a portion of the visual cortex (probably the striate cortex or area 17) as a function of spatial frequency. We found that there was a very high correlation between reaction time and the latency of the neuromagnetic response (21). This held for a wide range of latencies, varying from 80 to about 150 msec depending on spatial frequency. In fact, virtually all of the increase in reaction time with spatial frequency could be accounted for by the increase in the latency of the response of the primary visual cortex to the stimuli.

In a follow-up study, Okada et al. (11) varied the contrasts of the patterns as well as their spatial frequencies. In a pattern of low contrast, there is a smaller difference between the luminances of the bright and dark bars than there is in a pattern of higher contrast. We found that latency increased as contrast became lower, but this increase was the same regardless of spatial frequency. We also measured simple reaction time to these same patterns using the same human subjects and found a similar increase in reaction time. By subtracting the latency of the response of the visual cortex from the overall reaction time, it is possible to determine the interval of time required to complete an overt

response to a pattern after it evokes activity in the sensory cortex of the brain. This interval includes the time required for actually executing the response as well as the time required by the brain for processing the input prior to the initiation of the response. This "decision plus motor response" time was about 115 msec.

It will be recalled that we also performed an experiment in which we detected activity of the motor cortex prior to finger flexion in response to the appearance of a visual pattern. This pattern was also a simple bar grating, and it had a spatial frequency of 1 cycle per degree of visual angle. The overall reaction time to such a pattern is about 200 msec. We found that the motor cortex became active about 50 msec prior to initiation of the finger motion. Let us assume that the actual release of the button requires, roughly, 40 msec for completion. Subtracting this motor response time (40 msec) and the time between onset of activity of the motor cortex prior to the overt response (50 msec) from the overall reaction time of 200 msec leaves us with about 110 msec to account for. If about 85 msec of this period can be accounted for by the latency of the visual cortex, we are left with about 25 msec between the peak magnetic response of the visual cortex and the onset of activity of the motor cortex as the period within which the visual signal is processed and a decision made to react. One of our long-term goals is to vary the difficulty of this type of task and thereby manipulate the duration of this period within which cognitive processes are underway. We could then seek out those portions of the brain that become active during these processes. However, for now we must be satisfied with laying the foundations for such work by dealing with well known phenomena that have already been linked to various parts of the brain. This is the best way to evaluate our methods,and assess their ability to resolve localized sources so that their functional properties can be studied.

Thus far we have described some of the results we have obtained in studies of the cerebral cortex. One motive for this work is that, although physiologists and psychologists already know a great deal about this portion of the nervous system, there are other important and complicated portions of the brain about which less is known. As it happens, the neu-

romagnetic method has proven useful in the study of noncortical structures. and this is one of the main focuses of our present activities.

Psychophysiologists have been concerned for some time with "event related potentials" (ERP). These are to be contrasted with sensory EP. because they will occur even in the absence of sensory stimulation. e.g.. when an expected event does not occur. One of the most important of these ERP is known as *P300*. because it is an electrically positive wave when detected at the top of the head. and it occurs about 300 msec after certain kinds of events. In the classic experiments dealing with this phenomenon. two kinds of events are presented in a random sequence. One of these events occurs relatively rarely, and is therefore known as an "oddball" event. Typically. a wave appears in the averaged EEG between 300 and 500 msec after the subject detects an oddball. and the wave is either absent or much smaller in amplitude after the more frequent and "expected" event. ERP researchers are generally convinced that P300 is related to certain kinds of cognitive activity. One of the main interests in this field is the location of the source or sources of P300.

Halgren et al. (9) utilized the oddball method in patients undergoing brain surgery with electrodes implanted deep within their brains. They found that large potential gradients were present in the vicinity of the hippocampal formation and amygdala a few hundred msec after the presentation of an oddball stimulus. which the subject had to detect and count. This suggested that P300 might well have a subcortical origin in one or more of the nuclei comprising the limbic system. Other evidence suggests that the hippocampal formation is involved in memory. and P300 might well be associated with the transfer of information between short-term and long-term memory. These findings are clues to the location and orientation of the source of P300. which should be deep within the brain and capable of being represented by a current dipole oriented more or less vertically. Based on these considerations. our group implemented an oddball experiment and mapped the neuromagnetic field about the head. It was found that it is possible to pick up a neuromagnetic counterpart to the electrical P300 and related components of the ERP. Over the left hemisphere. the field emerged from the

side of the head and reentered in the occipital region. Also. a similar field emerged from the right occipital area and reentered the head on the right side anterior to the ear. After a painstaking experiment involving many measurements taken over several days. Okada. Kaufman. and Williamson (12) found that it was possible to create maps of the field associated with several of the components of the ERP. These maps made it possible to determine the location within the head of an equivalent current dipole that would give rise to them. The source of the magnetic "P300 complex" was in or near the hippocampal formation.

The fact that neuromagnetic sensors make it possible to detect activity originating in the deeper recesses of the brain might well be of clinical value. For example. Ricci et al. (14) discovered that some victims of Jacksonian epilepsy exhibited paroxysmal magnetic fields and that some of these patients had negative EEG. CT scan. and angiograms. Subsequent surgery revealed the presence of small tumors. Barth et al. (1. 2) were successful in locating tumors underlying epileptiform phenomena by averaging the magnetic field using the interictal spikes of the EEG as reference signals. Recently. Sutherling et al. (16) stated that this procedure leads to localization of foci with an accuracy of 1 cm in stereotaxic coordinates. However. one of the obstacles still to be overcome is that it now requires long periods of time to map a neuromagnetic field.

The studies described above support the view that neuromagnetic measures might well come to complement the classic sensory evoked and event related potentials. It is conceivable that the joint use of electrical and magnetic measures will enable us to resolve the radial and tangential components of sources underlying observed fields and potentials. Also. if locating and resolving sources of neuromagnetic fields is somewhat simpler than the localization of the same sources of EP. then it might be possible to utilize magnetic data in identifying sources that contribute to complex EP wave forms. This will enhance our ability to interpret EP. Also. some magnetic measures might well give us information about activity of different sources in the brain that cannot be unambiguously determined from electrical measurements. Finally. the magnetic field

measures appear to have some value in the study of epilepsies that have thus far eluded EEG studies. Perhaps similar advantages will be found in other clinical conditions.

Before we can reach such a goal. it is essential to recognize that all the data described in this chapter are based on measurements using a single sensor. To obtain field maps. the sensor had to be moved to as many as 80 different positions. and the field measured at each position several times. This procedure entails a number of assumptions. not the least of which is that the activity of the brain is relatively stationary from measure to measure. This is probably not a valid assumption. Hence the most important development for the future is that of multisensor arrays that would be capable of measuring the field at several places at the same time. We have already made a beginning in achieving this goal.

We now have a five-channel neuromagnetometer installed in our laboratory. and it is being used to map magnetic fields external to the scalp. By using this system. we have facilitated the mapping process very substantially and have already discovered effects that we could not have discovered using the single channel system. These will be described in future communications. This system is the precursor of other even more advanced systems that will permit a much more rapid scan of the magnetic field external to the head. Furthermore. the basic technology available for recording very weak magnetic fields is proceding along with the development of multisensor arrays. For example. our five-channel neuromagnetometer includes dc-SQUIDs that are an order of magnitude more sensitive than the rf-SQUID used in our earlier systems. SQUID sensitivity is no longer a limiting factor. Also. the dimensions of the second-order gradiometer were changed to improve its sensitivity to sources lying deep within the brain while not compromising its ability to respond to the more superficial cortical sources. which we have spent most of our time studying. We look forward to the day when large-scale arrays will make it possible to create functional three-dimensional maps of the brain in real time.

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